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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/574,125	06/13/2006	Per Holm	20481/0206897-US0	5556

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EXAMINER	
WESTERBERG, NISSA M	
ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
12/15/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,125	HOLM ET AL.	
	Examiner	Art Unit	
	Nissa M. Westerberg	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2 - 23, 36, 39 - 41, 43, 45 - 51, 53 - 57, 59, 66, 71 - 90* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2 - 23, 36, 39 - 41, 43, 45 - 51, 53 - 57, 59, 66, 71 - 90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 7, 2009 has been entered.

Applicants' arguments, filed October 7, 2009, have been fully considered but they are not deemed to be fully persuasive. The following rejections and/or objections constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 2 – 23, 36, 39 – 41, 43, 45 – 51, 53 – 57, 59, 66 and 71 – 85 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear what actions are carried out in optional step ii) of claim 59. This

step recites “bringing the first composition in liquid form”. It is unclear if something is being brought from one location to another or if the materials are brought into a particular state, such as a liquid state, as in the phrase “bring the water to a boil”. Please clarify.

4. Claim 74 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 59, from which claim 74 depends, requires that the release modifier is added to the composition by dry mixing (step v). However, claim 74 requires that the release rate modifier be added in a fluid bed. Fluid bed apparatus use a constant stream of air to suspend particles, to which liquids are sprayed onto the particles and stick. It is unclear how the dry mixing required by claim 59 and this addition taking place in a fluid bed do not appear compatible. Please clarify.

Response to Arguments

5. Applicant's arguments with respect to the art rejections of the claims have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 2 – 23, 36, 39 – 41, 43, 45 – 51, 53 – 57, 59, 66 and 71 – 90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holm et al. (WO 03/004001) in view of Yamashita et al. (US 6,576,259) and the Merck index entry for tacrolimus.

Holm et al. discloses a process of preparing compositions comprising a therapeutically and/or prophylactically active substance with improved *in vitro* dissolution and/or shelf life (p 1, ln 5 – 13). This process demonstrates very promising results with respect to bioavailability when the process is employed with active substances that have a very low aqueous solubility (p 12, ln 5 – 8). This particulate material is prepared by a process in which a first composition, a carrier in a liquid form with a melting point of about 5°C or higher, is sprayed on a second composition, whose temperatures is at or below the melting point of the carrier of the first composition, and then mechanically working the second compositions after the second composition has been sprayed with the first composition (p 1, ln 33 – p 2, ln 14).

The carrier described by Holm et al. corresponds to the first composition of the instant claims. Suitable carriers include hydrophobic carriers that are normally used in the manufacture of a modified release pharmaceutical (p 3, ln 25 – 27, 34 – 35). Specific examples of suitable hydrophobic carriers are given on p 4, ln 19 – 28. The carrier can further comprise additional carriers, surfactants (surface active agents), one or more therapeutically and/or prophylactically active substances and/or one or more pharmaceutically acceptable excipients (p 6, ln 13 – 19). Other additives can include antioxidants and stabilizing agents (p 8, ln 20 – 27). The viscosity of this solution must be suitable so that it is not so thick as to clog the delivery nozzle (p 9, ln 21 – 25).

Generally, the viscosity of the carrier is at the most 800 mPas at a temperature of at most 100°C (p 9, ln 25 – 31). In the resulting material, the concentration of the carrier can vary widely, from about 5% to about 95% w/w with many intermediate ranges disclosed (p 9, ln 33 – p 10, ln 5).

It is not required that an aqueous process be used, and the agglomeration process can take place under water-free or substantially water-free conditions (p 10, ln 33 – p 11, ln 8).

The active substances suitable for use in the particulate matter is broad, and encompasses drug substance, hormones, genes or gene sequences, antigen-comprising material, proteins, peptides, vitamins, minerals, lipids, carbohydrates and mixtures thereof (p 11, ln 19 – 28). Compounds with a variety of degrees of water solubility at 25°C and a pH 7.4 are also suitable for use in the instant invention (p 12, ln 8 – 16).

The second composition should be at a temperature that is lower than the melting point of the first solution (p 20, ln 11 – 19). The second composition can comprises pharmaceutically and/or cosmetically acceptable excipients and/or therapeutically or prophylactically active substances (p 21, ln 1 – 3). As shown in examples 1 and 2 (p 31 – 36), lactose is used as the solid second composition onto which the liquid first composition is applied. The excipients can include fillers, diluents, disintegrants, binders, lubricants, acidifying agents, alkalizing agents, antioxidants, buffering agents, coloring agents solubilizing agents and flavors (p 21, ln 12 – 20).

Among the exemplified filler, diluents and binders are release rate modifiers such as hydroxypropylmethyl cellulose (HPMC; p 21, ln 22 – p 22, ln 2).

The process can be carried out in a high or low shear mixer or in a fluid bed (p 23, ln 29 – 30). The carrier is heated to a temperature above the melting point (p 23, ln 32 – 33). Normally, the spraying is performed through a spraying device equipped with a means to control the temperature (p 25, ln 17 – 18). The material obtained by this process general has a geometric weight mean diameter of ≥ 10 μm but can be larger (p 25, ln 20 – 28). The particulate matter is excellent for further processing (p 26, ln 6 – 10) and can be coated with a variety of coatings, including a film coating, modified release coating, protective coating or enteric coating (p 26, ln 12 – 14).

Relevant pharmaceutical preparations made using the particulate material can be solid, semi-solid, or liquid (p 27, ln 20 – 23) and take form such as tablets (p 27, ln 28).

For example, tablets are produced by first heating a combination of polyethylene glycol (PEG) 6000 and poloxamer 188 to 75°C and the model drug substance was dissolved in the PEG 6000 and poloxamer 188 to form the first liquid composition which was then sprayed onto a microcrystalline cellulose solid second composition ("treatment B", p 40, ln 27 – p 42, ln 6). PEG 6000 is a polyethylene glycol having an average molecular weight of from 3,000 to 35,000.

Holm et al. does not disclose the inclusion of tacrolimus as an active agent or information about the release profile of the drug from the composition. Holm et al. also does not explicitly disclose the addition of a release-rate modifier, such as HPMC, to the resulting composition by dry mixing.

Yamashita et al. discloses sustained release formulations of tacrolimus or its hydrate in which release of 63.2% of the drug occurs is dissolved with 0.7 – 15 hours (col 1, ln 45 – 50), with the most preferred formulation releasing this amount in 2 – 5 hours (col 3, ln 28 – 30). While the tests in Yamashita et al. use a 0.005% HPMC aqueous solution and 50 rpm paddle speed, there is no evidence that the release profile required in the instant claims as measured under slightly different conditions required by the instant claims will not meet the dissolution profiles, such as less than 85% release within about 6 hours after the start of the test. Solid particles containing the macrolide compound (such as tacrolimus, FK506) can be prepared and the lubricants, excipients and the like can be added if necessary (col 11, ln 14 - 17). The resulting mixture can be mixed together to form the sustained release formulation (col 11, ln 40 - 48). In example 12 (col 19), molten glycerin stearate, tacrolimus and HPMC 2910 are formed into solid particles. In Example 16 (col 21), the solid material was generated by a different process that was then dry-mixed with lactose and filled into a capsule.

Tacrolimus is a drug with a melting point of 127 - 129°C and is insoluble in water (Merck index entry for tacrolimus).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to use the disclosed process of Holm et al. to prepare a dosage form of the water insoluble drug tacrolimus with the claimed release profile, as taught by Yamashita et al. Holm et al. discloses that the process and use of excipients such as a combination of PEG 6000 and poloxamer 188 increases the bioavailability of active

agents with very low aqueous solubilities, and tqacrolimus is one such agent (Merck index entry).

Yamashita et al. discloses information regarding desired release profile of macrolide active agents such as tacrolimus so one of ordinary skill would optimize the ingredients and amounts of those ingredients to provide the desired release profile while improving the bioavailability of this water insoluble drug using the method and formulations disclosed by Holm et al. Yamashita et al. discloses that excipients such as lactose can be added to the solid particles containing active ingredient while Holm et al. discloses that HPMC and lactose are functionally equivalent in that both ingredients act as fillers, diluents and/or binders (col 21, ln 22 – 30). The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient to add in order to best achieve the desired results, such as the sustained release profile and a material that can be further processed into forms such as tablets.

In regards to claims 79, 80 and 88 which require that the PEG, poloxamer and HPMC form a matrix, the cited prior art teaches the same method for preparing a solid composition of tacrolimus as recited by the instant claims. The formulation made by the cited prior art must necessarily result in the formation of a matrix as the same

ingredients are used in the same process and as such, cannot result in the formation of a different structure (i.e., matrix).

The selection of order of performing process steps, such as the stage at which the release-rate modifying substance is added is *prima facie* obvious in the absence of new or unexpected results (MPEP 2144.04 IV C). One of ordinary skill in the art would determine the optimal order of steps based on the desired location of the various ingredients in the final dosage form and the appropriate equipment to carry out those steps from the equipment known in the art, such as high or low shear mixture or a fluid bed apparatus to provide the best mixing of the various ingredients.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nissa M. Westerberg whose telephone number is (571)270-3532. The examiner can normally be reached on M - F, 8:00 a.m. - 4 p.m. ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jake M. Vu/
Primary Examiner, Art Unit 1618

NMW